Clinical review

Drug intake during Ramadan

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During Ramadan, the ninth month of the Islamic lunar calendar, adult Muslims are required to refrain from taking any food, beverages, or oral drugs, as well as from sexual intercourse, between dawn and sunset. Ramadan can occur in any of the four seasons, and the hours spent fasting vary accordingly from 11 hours to 18 hours a day. Rhythms of life and habits during this fasting period differ from one country to another. In Morocco, two to three meals daily are eaten within a short overnight span during this month. The first meal might be taken immediately after sunset (Iftar) and the second one around three hours later (dinner); the last meal might be taken shortly before dawn (Sohour). Intake of drug doses is therefore not easy, and its adjustment to the life rhythm of Ramadan is often not rational.

Aslam et al surveyed 81 patients to determine the alterations they made to their drug regimens during the fasting period of Ramadan.¹ They found that 42% of the patients adhered to their usual treatment, and 58% changed their intake pattern. Among the second group, 35 patients stopped their treatments, eight changed the administration schedule, and four took all the daily doses in one intake. Another survey of 325 outpatients in a Kuwaiti hospital found that most of them changed their drug regimens during Ramadan.2 Sixty four per cent of the patients changed their therapeutic scheme during the month; 18% took their daily medicines in a single intake, either before the first meal (sunset) or straight after the last one (before dawn). The authors warned about the high risk of drug interactions in such cases. In fact, a 57 year old woman with heart failure experienced side effects of digitalis after being treated with both a thiazide diuretic and a digitalis compound. According to the authors, the concomitant intake of those two drugs induced a drop in potassium following a diuretic induced decrease in water retention, which led to an increase in sensitivity of heart muscle to digitalis.

Wheatly and Shelly reported that two patients with chronic reversible respiratory disease were admitted to an intensive care unit two weeks after the start of Ramadan. Both patients subsequently admitted to not having taken their treatment, including inhalers, during daylight hours.³ A prospective study evaluated the changes in frequency of seizures during Ramadan in 124 patients with idiopathic epilepsy. Seizures occurred in 27 patients during this month; 20 of them did not use any antiepileptic drugs from dawn to sunset. The author concluded that withdrawal of drugs

Summary points

Ramadan, a month of fasting, is a daily abstinence from any food, beverage, or oral drug from dawn to sunset

Patients with chronic diseases often insist on fasting even though they are permitted not to by Islamic rules

Patients with acute diseases would similarly be allowed to stop fasting and make up for it after Ramadan

Several studies have shown that patients arbitrarily change the intake time and dosing of drugs without taking medical advice

This behaviour could alter the pharmacokinetics and pharmacodynamics of drugs, especially those with a narrow therapeutic index, and consequently their efficacy and tolerance

was the most important cause of recurrence of epilepsy during Ramadan.⁴

The main emphasis of the authors of these studies was that most of the patients did not receive any particular information about changing their treatment during Ramadan. In the face of this arbitrary use of drugs during Ramadan, drug intake needs to be adapted according to the prescription components—the route of administration, the rhythm and schedule of administration, and interaction with food intake. In this paper we review current knowledge on this subject.

Sources

To build up this review, we used our own knowledge, experience, and previous publications on the subject of drug intake during Ramadan. We also searched Medline and consulted several websites.

Route of administration

The compatibility of fasting with the various drug administration routes and their choice during Ram-



Extra references are on bmj.com

adan remain a matter for the doctor's own judgment. To settle differences in point of view and standardise the choice of routes, a religious-medical seminar entitled "An Islamic view of certain contemporary medical issues" was held in Morocco in June 1997; one of the main topics discussed was the substances and actions that nullify fasting. The participants—distinguished Muslim jurists and religion experts, medical practitioners, pharmacologists, and specialists in other human sciences—agreed unanimously that the following administration routes do not nullify fasting⁵:

- Eye and ear drops
- All substances absorbed into the body through the skin, such as creams, ointments, and medicated plasters
- Insertion into the vagina of pessaries, medical ovules, and vaginal washes
- Injections through the skin, muscle, joints, or veins, with the exception of intravenous feeding
- Oxygen and anaesthetic gases
- Nitroglycerin tablets placed under the tongue for the treatment of angina
- Mouthwash, gargle, or oral spray, provided nothing is swallowed into the stomach.

A majority of participants added:

- Nose drops, nose sprays, and inhalers
- Anal injections
- Surgery involving general anaesthesia, if the patient decided to fast.

Dosing schedule

Dosing schedules have to be altered during Ramadan. In fact, drug doses can be taken only between sunset and dawn, and the time span between them is shorter than outside Ramadan. Two different types of dosage schedule are commonly used during Ramadan.

Single daily dose

The easiest situation is that of patients who have a usual evening dose. Their therapeutic scheme remains unchanged during Ramadan, as it does not interfere with fasting. When the usual intake is in the morning or during the day, the doctor must be careful when delaying the intake to the evening that this will not alter the efficacy of treatment or the tolerance of the drug.

The efficacy and toxicity of many drugs can vary depending on the time of administration in relation to the circadian rhythms of biochemical, physiological, and behavioural processes. Thus, circadian time has to be taken into account as an important factor influencing a drug's pharmacokinetics or its effects or side effects. Table 1 summarises the results of some chronopharmacokinetic and pharmacodynamic studies for selected drugs. W1-w12

Few studies have investigated this subject in relation to Ramadan. A comparative study of the pharmacokinetics of theophylline before and during Ramadan in healthy volunteers showed a significant decrease in the amount of drug absorbed for the 8 pm intake (two hours after Iftar) compared with the 4 am intake (immediately after Sohour). This result was mainly explained by the changes in the circadian variations of the gastric pH and by the modifications of rhythms and quality of meals during Ramadan.

 Table 1
 Selected drugs with circadian variation in pharmacokinetics and pharmacodynamics

pharmacodynamics				
Drug	Variation			
Propranolol	Absorbed more rapidly after morning dosage than after night dosage.** 1 However, chronokinetics cannot explain circadian changes in effects. Circadian variation in sympathetic tone and vascular reactivity is mainly responsible for circadian changes in effects of propranolol** 2			
Nifedipine	Pharmacokinetics of immediate release but not sustained release preparation depends on time of day. Immediate release nifedipine had higher C_{\max} (peak concentration) and shorter t_{\max} (time to peak concentration) after morning dosing than after evening dosing, and bioavailability in the evening was reduced by about $40\%^{\text{mos}}$			
Digoxin	Time to reach maximum plasma concentration was significantly shorter after 8 am dosing (54 min) than after 8 pm dosing (96 min) $^{\rm w4}$			
Diltiazem	Diltiazem HCl extended release tablets administered in the evening (10 pm) had 17% and 22% greater bioavailability than morning administration (7 am or 8 am) under single dose and stea state conditions, respectively $^{\text{w5}}$			
Enalapril	Subchronic treatment at 7 am significantly reduced blood pressure during the day but was less effective at night. Subchronic dosing at 7 pm significantly decreased night time blood pressure followed by a slow increase during the day, with no effect on elevated afternoon values ^{w6}			
Theophyllin	entake of a timed release formulation of theophylline at 3 pm achieved therapeutic drug concentrations during the night and avoided toxic concentrations during the day. **A new asymmetric dosage regimen of sustained release formulation of theophylline glycerinate (one tablet in the morning and four tablets in the evening) produced a steady and effective concentration of theophylline in plasma for the whole day, especially in the evening**			
Inhaled steroids	Optimal once daily dosing of inhaled steroid is between 3 pm and 5 30 pm ^{w9}			
Prednisone	Oral prednisone has been shown to be much more effective in improving several features of nocturnal asthma when administered at 3 pm rather than at 8 $\rm am^{w10}$			
Cimetidine	Administration of H_2 antagonists at bedtime is more effective than administration in the morning. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence ^{w11}			
Ibuprofen	After administration of ibuprofen press coated formulation, both the rate and extent of absorption were lower when dosing took place at 8 am than when dosing took place at 10 pm. The difference between morning and evening dosing of the immediate release formulation was minimal ^{w12}			

A similar study on the pharmacokinetics of valproic acid in healthy volunteers showed a significant influence of the alterations to life rhythm and administration schedule on the pharmacokinetic parameters of this drug. In addition to the delayed absorption phase for the 8 pm intake during Ramadan, the main impairment was a significant decrease in the plasma elimination half life for the 5 am intake compared with the same intake time outside Ramadan. As this parameter determines the administration schedule, it would be relevant to monitor the use of this antiepileptic drug during Ramadan.

Studies on antihypertensive drugs have not shown any significant effect on their efficacy from either the Ramadan life rhythm or the changes in administration schedule.9 10 These studies were done in patients with high blood pressure and treated by once daily preparations, before and during Ramadan. All patients in these studies continued their drugs during Ramadan. The results of ambulatory blood pressure monitoring in the first study did not show any significant differences between the periods before Ramadan and during Ramadan in systolic pressure, diastolic pressure, 24 hour pressure, diurnal pressure, or nocturnal pressure.9 However, the authors observed that during the month of Ramadan the peak of the awakening is delayed by two hours and the nocturnal trough is delayed by one hour. The administration schedules in this study were not the same in the two time periods. The patients took their drugs at 8 am outside Ramadan and at the break of fasting (7-8 pm) during Ramadan. Perk et al reported similar results of 24 hour blood pressure monitoring before Ramadan and during the last week of Ramadan in 70 hypertensive patients, all of whom continued their once daily antihypertensive drugs during Ramadan.10 No significant differences



Fasting from dawn to dusk during Ramadan could cause problems with drug dosage regimens for Muslim patients

were found between mean blood pressure or blood pressure load before and during Ramadan. The authors of both studies concluded that in patients with essential hypertension without complications, fasting during the month of Ramadan can be safely undertaken with continuation of previous drug treatment.

Saour et al evaluated, over a period of five years, the efficacy and tolerance of a long acting oral anticoagulant in two groups of patients. During this period, the 106 patients in the first group made the Ramadan fast, whereas the 183 patients in the second group did not fast. All the patients in the first group took their drugs at night rather than during the day. The incidence of thromboembolic events and haemorrhagic complications did not differ significantly between the two groups. The authors concluded that Ramadan fasting has no adverse effects on the efficacy and safety of long term oral anticoagulant treatment.

Two or more daily doses

During Ramadan, accurate distribution of drugs prescribed twice a day is difficult to achieve between the break from fasting and the beginning of fasting. Refraining from fasting according to the Islamic rules could be a wiser prescription. Nonetheless, patients with two doses could take the first one at the break of fasting and the second one before the beginning of fasting, in which case the dosing time and the time span between the doses are both altered. These alterations could affect the drug's plasma concentration profile and, therefore, its efficacy and tolerance. This is even more relevant for drugs with a narrow therapeutic index as the risk of toxicity is higher.

In fact, Daghfous et al reported an influence of fasting on the pharmacokinetics and side effects of a sustained release preparation of theophylline taken twice a day.¹² The study included 12 patients with current stable asthma and was done in two stages-the first stage was during Ramadan, and the second stage was four weeks after the end of Ramadan. In both periods, the patients received two oral doses of theophylline, one just before dawn (3 am) and the second at sunset (7 pm) for five days. Outside Ramadan, only four out of 12 patients reported adverse events of minor nausea. During the fast of Ramadan, eight out of 12 patients reported adverse effects of abdominal pain and nausea. Six of them had also vomiting; fasting was then interrupted. In these patients, the blood theophylline concentrations were moderately, but not significantly, higher than in the patients without marked gastrointestinal problems. The authors concluded that a longer acting preparation taken in a single daily dose, preferably at the end of the night, would be a solution for asthmatic patients during Ramadan

In the event of therapeutic problems during Ramadan, the number of doses should be reduced by using, when available, slow release formulations or chronothe rapeutic formulations. Verapamil hydrochloride (Verelan PM, Covera-HS), $^{\scriptscriptstyle 13}$ propranolol CR (Innopran XL),14 diltiazem hydrochloride (graded release diltiazem),15 and tulobuterol (tulobuterol transdermal therapeutic system),16 are some of the new chronotherapeutic formulations available. Otherwise, a drug with a longer elimination half life should be used. Such drugs will have a longer duration of action and can therefore be taken at longer intervals, such as once a day. This is the case with non-steroidal antiinflammatory drugs that are used for joint disease such as arthritis: ibuprofen (half life 2-3 hours), flurbiprofen (3-4 hours), naproxen (12-15 hours), and piroxicam (26-38 hours) are some examples. Patients who are prescribed drugs such as ibuprofen or flurbiprofen need to take doses three or four times a day to maintain a concentration of the drug in the body tissues sufficient to provide adequate pain relief. These drugs could be replaced by a single daily dose of piroxicam, which is more suitable for the fasting patient.17

Interaction with food intake

Generally, drug-food interactions may result in reduced, delayed, or increased systemic availability of a drug (table 2). w13-w26 The degree of interaction, and whether it positively or negatively affects drug absorption, depends on several factors, including the physical and chemical nature of the drug, the formulation, the type of meal, and the time interval between eating and dosing. The last two factors could have an enhanced effect during the month of Ramadan, as the rhythm and composition of meals are modified. In Morocco, an average of three meals are served between sunset and dawn. The first one is taken immediately after sunset and contains an important amount of fat and carbohydrates; the second one, containing mainly animal proteins, is taken three to four hours later. The last meal is taken between 30 minutes and one hour before sunrise and is a breakfast-like meal. Thus particular care should be taken when using drugs that have to be administered on an empty stomach, such as furosemide, rifampicin, and erythromycin.

The quality of the food eaten during the fast breaking meal could also have an influence on the absorption of some drugs. Beverages such as tea, coffee, and orange juice can increase gastric acidity, which increases the absorption of weak acids such as salicylates, dipyridamole, sulfamides, and some antibiotics and hypnotics; the action of pethidine, amitriptyline, and antihistamines may be inhibited. The high concentration of fat and carbohydrates at this meal could alter the bioavailability of drugs, but this alteration depends on the formulation used. For example, the intake of free acid phenytoin, as Hydantol powder, with a high fat meal increased its bioavailability, whereas the intake of an extended release pheny-

Table 2 Commonly encountered drug-food interactions and recommendations (outside Ramad	Table 2	Commonly encountere	d drug-food interactions and	recommendations	(outside Ramada
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Drug	Interaction	Recommendation	
Levothyroxine	Intake with food may decrease absorption. ^{w13} High fibre diets have been shown to decrease levothyroxine absorption. ^{w14} Levothyroxine absorption is increased when it is taken on an empty stomach ^{w15}	Thyroid hormones should be taken an hour before eating, at the same time every $\mbox{day}^{\mbox{\tiny wr} 14}$	
Digoxin	High fibre foods, such as whole wheat products, raw vegetables, bran cereal, and fruits, inhibit absorption of digoxin and decrease its effect**16	To avoid this problem, patients should take digoxin one hour before food or two hours after eating $^{\rm w17}$	
Verapamil/felodipine	Ingestion of grapefruit juice has been shown to increase absorption of verapamil $^{\text{w17}}$ and felodipine $^{\text{w18}}$	In order to prevent side effects of these drugs, patients who are taking verapamil or felodipine, or similar drugs such as amlodipine and nifedipine, should avoid grapefruit and its juice ^{w17} w18	
Propranolol	High protein foods may interfere with propranolol metabolism by increasing blood concentrations and activity of propranololw19		
Lithium	Foods that alkalinise the urine may increase elimination of lithium from the body, potentially decreasing its actions $^{\rm w17}$		
Theophylline	A diet low in carbohydrates and high in protein, as well as charcoal grilled beef, increases elimination of theophylline, resulting in poor control of asthma and other conditions. Therefore, a high carbohydrate, low protein diet will halt elimination of theophylline, leading to optimal therapeutic effect**20	Food can have different effects depending on the dose form. Sustained release forms of theophylline should be taken on an empty stomach. Liquid and non-sustained release theophylline products are best taken on an empty stomach, but they may be taken with food if stomach upset occurs ^{w20}	
Loratadine	Food slows the absorption of loratadine and also increases the total amount absorbed ^{w21}	Loratadine should be taken on an empty stomach ^{w21}	
Fexofenadine	Ingestion of grapefruit juice, orange juice, or apple juice along with fexofenadine decreases its blood concentrations ^{w22}		
Carbamazepine	Grapefruit juice increases the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in gut wall and liver ^{w23}		
Diazepam	Substantial increase of absorption with grapefruit juicew24		
Bisphosphonates	Food substantially reduces the bioavailability of oral alendronate. **\footnote{n}^{25} \text{Taking alendronate either 60 or 30 minutes before a standardised breakfast reduced bioavailability by 40% relative to a two hour wait. Black coffee or orange juice alone, when taken with the drug, also reduced bioavailability (approximately 60%)**\footnote{n}^{25} \text{ (approximately 60%)**\footnote{n}^{26} (approximately 60%)**\fo	A practical dosing recommendation is that patients should take the drugs with water after an overnight fast and at least 30 minutes before any other food or beverage	

toin sodium formulation (Phenytek) with a high fat meal decreased its bioavailability.¹⁹

The clinical impact of such interactions depends on the narrowness of the drug's therapeutic index. An alteration in bioavailability as a result of these interactions could have a substantial effect on the plasma concentration of a drug, particularly a drug with a narrow therapeutic index, leading to reduced efficacy or increased side effects.

Conclusion

Extensive misuse of prescribed drugs during Ramadan may lead to therapeutic failures. The lack of survey data on this subject impairs effective evaluation of the problem. This lack of information is a problem for doctors, as they cannot give unbiased advise. Further studies should be carried out to provide more guidelines about the ways in which the administration of drugs should be modified. In the meantime, doctors and scientists in the Muslim world should be encouraged to follow up their patients with chronic diseases during Ramadan, in order to establish optimal dosage regimens.

According to the data that are available, patients arbitrarily modify the times of doses, the number of doses, the time span between doses, and even the total daily dosage of drugs during the month of Ramadan, often without seeking any medical advice. Recommendations are not easy to make as the reliability of the available results remains questionable. In fact, most of the studies carried out during Ramadan were retrospective, and small samples were often used. Other methodological errors were also seen, such as incomplete descriptions of the therapeutic schemes observed before and during Ramadan. In order to make an objective comparison of the results obtained before and during the month of Ramadan, the administered doses, the number of daily doses, and the administration times need to be shown for the two periods studied. For patients with chronic diseases, the new dosage regimen to be used during Ramadan needs to be established beforehand. Patients must also be informed about when they should take their drugs (before, during, or after food intake), particularly when they are treated with drugs of which the absorption could be impaired by food intake.

The best reference period for comparison with Ramadan would be the period before Ramadan rather than that immediately afterwards. Ramadan is characterised by repeated fasting and altered life habits that last four weeks, and its influence on chronobiological parameters can last beyond the end of the month of Ramadan.

The choice of drugs to be studied during Ramadan could be determined by surveys evaluating the therapeutic problems encountered during this month of fasting. Focus should be on drugs for chronic diseases, and especially on those with a narrow therapeutic index. Wide dissemination of research results, as well as achievement of consensus on relevant clinical and therapeutic issues, would allow health professionals throughout the Muslim world, and in countries with an important Muslim population, to provide accurate and standardised advice on the appropriate use of drugs during the holy month of Ramadan.

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Additional educational resource

Islam Set (www.islamset.com)—Includes responses to questions on a variety of Islam related science subjects

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Interactive case report

A 35 year old woman with diabetic nephropathy who wants a baby

This case was described on 18 and 25 September (BMJ 2004;329: 674, 729). Debate on the management of the patient continues on bmj.com (http://bmj.com/cgi/eletters/329/7467/675). On 14

October we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from the patient and relevant experts.

The practicable paradox—the five minute emergency

At our surgery, each doctor offers four slots of five minutes each at the end of the morning for "genuine emergencies." The other day I found myself whingeing to a colleague about the banal nature of complaints that patients often bring to these appointments. On one particular day the first patient wanted a sick note, the second had run out of paracetamol, another wanted to chase a physiotherapy referral that hadn't come through, and the last was a chap with an itchy burn. Each consultation ended with some gentle patient education. Admittedly, a small part of me was thankful that these weren't hugely taxing appointments, but I was mostly annoyed that these slots should have been reserved for more deserving emergencies.

Then it struck me that I couldn't actually name more than a handful of things that would actually qualify as GP emergencies that could be dealt with in a five minute slot. In fact, what is a GP emergency? If your arm is hanging off after an accident, then you need to get to casualty pretty quickly. The "morning after" pill can be bought over the counter or is available free of charge at community clinics. The advent of the new local NHS walk-in centre should be able to see to sore throats and earaches, and repeat medication should be asked for in advance. So what is a reasonable five minute emergency? Indeed, is there such a thing? Suspected appendicitis would be reasonable; so would cellulitis or a mother sick with worry over her feverish toddler. All of these seem reasonable to me.

The trouble is that most real emergencies hardly ever take five minutes to sort out. One evening, during my "duty doctor" five minute slots, I saw a pregnant woman who was bleeding heavily, a feverish 6 week old baby with poor feeding, a woman who was actively suicidal, and then a woman with slurred speech and incontinence. The time taken to make an assessment of each patient, to document everything, to arrange admission, and then to write a referral letter was in the order of 20 minutes. I sometimes find it incredible that my predecessors were used to routine appointments of six minutes. Perhaps I'm expecting too much. The five minutes that are allocated are effectively nominal. I can't recall many clinics, in hospital or the community, that run to time.

After all of my pontificating and efforts at patient education, I am sure of only one thing-that, with recent changes in our profession, medical law, and the way that people's health expectations have changed in the past few decades, I for one cannot clearly define the realms of what constitutes a genuine five minute emergency in general practice. So can I honestly expect

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